REMARKS

Claims 1, 3, 5, 7 and 9-11 are pending in this application. Applicants have by this Amendment amended claims 1, 3, 5 and 7, canceled claim 9 without prejudice, and added new claims 44-49. Thus, claims 1, 3, 5, 7, 10-11 and 44-49 are currently pending in the subject application.

Applicants have canceled claim 9 and have amended claims 1, 3, 5 and 7 solely to expedite the prosecution of the subject application to patent. Applicants, however, do not relinquish their right to claim or otherwise pursue patent coverage for the canceled or deleted subject matter.

Rejection under 35 U.S.C. § 112, first paragraph -written description

On pages 2-4 of the November 8, 2001 Office Action, the Examiner rejected claims 1, 3, 5 and 10-11 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons as set forth in the previous Office Action.

In response, to expedite prosecution of the subject application, but without relinquishing their right to claim or otherwise pursue patent coverage for the canceled or deleted subject matter, applicants have amended the claims to incorporate the limitation of claim 9 into claim 1. Since claim 9 was found to meet the written description requirement, applicants submit that amended claim 1 and all claims dependent thereon also meet the written description requirement.

Accordingly, the foregoing rejection on written description grounds should be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph - enablement

On pages 5-12 of the November 8, 2001 Office Action, the Examiner rejected claims 1, 3, 5, 7 and 9-11 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons set forth in the previous Office Action.

The Examiner responded to applicants' August 13, 2001 arguments by initially asserting that there is no evidence of record indicating that any Eo protein of the present invention is capable of binding the same E2 envelope protein epitopes that are thought to be responsible for cell attachment.

In response, initially, applicants clearly state in their specification that the E2 epitopes tested are those thought to be responsible for cell attachment. As the CAFC has reminded Examiners, "it is incumbent upon the Patent Office, whenever a rejection on this [enablement] basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). M.P.E.P. 2164.04. The Examiner did not provide any explanation for requiring applicants to support with evidence their presumptively accurate disclosure.

None the less, to expedite prosecution, applicants respectfully direct the Examiner's attention to page 18, lines 26-28 of the subject specification where preparation of the E2 protein construct is described as being based on the known sequence that

has been described in reference "7", which corresponds to Choo et al., *PNAS* (1991). Rosa et al. refer to the same known sequence and the same reference on page 1759, left column, in the second full paragraph, and then use that same sequence to make the E2 protein they studied. A copy of the Rosa et al. paper is attached as **Exhibit A** for the Examiner's convenience. Thus, it is clear that applicants' protein does indeed bind the same E2 protein epitope thought to be responsible for cell attachment.

The Examiner further asserted that there is no evidence of record indicating that any Eo protein of the present invention is capable of disrupting the formation of the E1 and E2 heterodimeric complex that is thought to be necessary for HCV binding and entry to the cells.

In response, applicants respectfully submit that one skilled in the art would reasonable expect that if the E2 envelope protein is bound to an extraneous protein, like Eo, then E2 could not bind to E1 to form the heterodimeric complex. The Examiner offers no explanation or reasoning for doubting that Eo, when bound to E2, would prevent E2 from binding to another protein, e.g. E1. Yet, it is incumbent upon the Examiner to explain why it is not reasonable to so expect before requiring applicants to provide "evidence". *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). M.P.E.P. 2164.04. Thus, applicants respectfully maintain that once the Eo protein binds to the E2 protein, which applicants have shown to take place *in vivo*, then it is reasonable to expect that the bound E2 protein cannot form a heterodimer with the E1 protein.

Then, in the paragraph bridging pages 13 and 14, the Examiner questioned whether binding to the E2 protein would prevent HCV from entering the cell. The Examiner proceeded to cite applicants' own discussion in the "Background of the Invention"

section of their application as support for the preposition that agents that bind to E1 and E2 have not been identified in the art as of the filing of applicants' invention.

In response, applicants admit to some confusion. Applicants' "Background of the Invention" section is directed at describing the state of the art *prior to their invention*. While agents that bind to E2 may not have been known prior to applicants' invention, applicants have found the Eo protein and its 120 amino acid variant that do bind to the E2 protein. Since applicants have provided in vivo data showing that the Eo protein and its 120 amino acid variant bind to E2, it is improper to question this.

To the extent the Examiner is questioning whether binding to the E2 protein inhibits cell attachment of HCV, applicants respectfully point out that Rosa et al. have shown, through *in vivo* studies, that binding the E2 protein inhibits HCV infection, not merely cell attachment. Furthermore, *Yi et al.*, Virology, 231:119-129, (cited by applicants on page 3, lines 19-21) have shown that a heterodimeric complex between E2 and E1 is necessary for HCV infection of cells. The Examiner has attempted to rebut these clear teaching of skilled artisans, along with applicants' statements which are based on a thorough understanding of the art, by relying on Flint et al. and WO 99/24054. A thorough review of Flint et al. and WO 99/24054, however, supports applicants' understanding of the function of E2.

In WO 99/24054, the Examiner cited page 2, lines 12-14, which read as follows, "the HCV envelope proteins E1 and E2 interact with each other to form hetero-dimeric complexes. Although the exact role of these HCV envelope proteins has not been elucidated yet, it has been suggested that they are responsible for binding of the virus to target cells." (Emphasis added). Applicants once

again admit to some confusion. WO 99/24054 clearly states that although the "exact" role of E2 has not been elucidated, what is known is that E2 is responsible for cell attachment. Indeed, WO 99/24054, in the very next sentence, acknowledges that, the "binding of E2 to target cells has been documented by several authors (Farci et al., 1996; Shimzu, et al., 1994; Zibert et al., 1995 and Rosa et al., 1996)."

In Flint et al., the Examiner refers to page 6782, column 2, last three lines, as the basis for questioning the teaching of applicants and of others. This section of Flint et al. reads as follows, "the mechanism by which HCV enters target cells is currently unknown; however, the E2 [glycoprotein] is thought to be responsible for initiating virus attachment to a receptor on potential host cells." (Emphasis added). Then on page 6788, column 2, last 7 lines, Flint et al. state that sera from chimpanzees immunized with homologous HCV glycoproteins inhibited cell entry of E2 expressing pseudotyped viruses that were otherwise able to enter the cells. Of course, sera from chimpanzees immunized with HCV glycoproteins would have antibodies to the E2 protein, as shown by Rosa. Thus, not only does Flint et al. fail to rebut applicants' teaching, Flint et al. support applicants' teaching.

Therefore, the Examiner's cited references Flint et al. and WO 99/24054, fail to support the Examiner's rejection. Importantly, at least one of the Examiner's cited references, Flint et al., actually supports the applicants' teaching and along with Rosa provides a reasonable correlation between applicants' *in vivo* examples and their claimed method.

In summary, the experiments in the subject application clearly show that the Eo protein binds with the HCV envelope protein E2. The E2 envelope protein of HCV has been shown to bind to the

plasma membranes of cells and this action of E2 mediates entry of the virus into the cells. E.g., D. Rosa et al., *PNAS* 93:1759-1763. Moreover, E2 and E1 envelope proteins form a heterodimeric complex, which has also been shown to be necessary for virus binding to the cells and entry into the cells. E.g., M. Yi et al., *Virology* 231:119-129. Antibodies that bind to E2 have been shown to prevent infection *in vivo*. E.g., D. Rosa et al. & Flint et al. With the Eo protein bound to the E2 envelope protein, the E2 protein would not be able to bind to the plasma membranes of cells or to form a heterodimeric complex with the E1 envelope protein. Accordingly, by binding the E2 envelope protein, the Eo protein is reasonably expected to block HCV attachment and entry into cells, similarly to the action of antibodies to E2.

Accordingly, the foregoing rejection on enablement grounds does not apply to the amended claims, and should be withdrawn.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Gary J. Gershik 2/8/02
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Claims with Revision Shown

10. (Twice Amended) A method of treating or preventing hepatitis C virus infection in a subject which comprises administering an effective amount of an Eo protein having amino acids 1-120 of SEQ ID NO:1 to the subject, wherein the Eo protein is capable of inhibiting the attachment of hepatitis C virus onto cells by specifically binding to the hepatitis C virus envelope E2 protein so as to treat or prevent hepatis C virus infection.

3. (Twice Amended) The method of claim 1, wherein the hepatitis C virus envelope E2 protein comprises amino acids having an amino acid sequence shown in SEQ ID NO:2 ~~(Figure 7)~~.

5. (Twice Amended) The method of claim 1, wherein the hepatitis C virus envelope E2 protein comprises amino acids having an amino acid sequence shown in SEQ ID NO:3 ~~(Figure 8)~~.

7. (Twice Amended) The method of claim 1, wherein the Eo protein comprises amino acids having the amino acid sequence shown in SEQ ID NO:1 ~~(Figure 2)~~.

~~9. The method of claim 1, wherein the Eo protein comprises an Eo1 protein having amino acids 1-120 of SEQ ID NO:1.~~

10. The method of claim 1, wherein the cells are liver cells.

11. The method of claim 10, wherein the liver cells are human liver cells.

44. (New) A method of preventing attachment of hepatitis C virus onto a cell, which comprises contacting the cell with an effective amount of an Eo protein having amino acids 1-120 of SEQ ID NO:1 to the subject, wherein the Eo protein is capable of inhibiting the attachment of hepatitis C virus onto the cell by specifically binding to the hepatitis C virus envelope E2 protein.

45. (New) The method of claim 44, wherein the hepatitis C virus envelope E2 protein comprises amino acids having an amino acid sequence shown in SEQ ID NO:2.

46. (New) The method of claim 44, wherein the hepatitis C virus envelope E2 protein comprises amino acids having an amino acid sequence shown in SEQ ID NO:3.

47. (New) The method of claim 44, wherein the Eo protein comprises amino acids having the amino acid sequence shown in SEQ ID NO:1

48. (New) The method of claim 44, wherein the cell is a liver cell.

49. (New) The method of claim 48, wherein the liver cell is a human liver cell.